FIP1L1-PDGFRα-Positive Hypereosinophilic Syndrome in Childhood: A Case Report and Review of Literature

Piero Farruggia, MD, Emilia Giugliano, PhD,† Delia Russo, MD,* Angela Trizzino, MD,* Roberta Lorenzatti, BA,† Alessandra Santoro, PhD,‡ and Paolo D'Angelo, MD**

Summary: Hypereosinophilic syndromes in children are rare disorders traditionally characterized by an eosinophil count exceeding 1,500/mm^3 on at least 2 occasions or evidence of tissue eosinophilia associated with symptoms and marked blood eosinophilia, lacking any secondary cause (such as infections, allergic disease, chemical-induced eosinophilia, hypoadrenalism, cancer). Until now there have only been 3 reported cases of pediatric FIP1L1-PDGFRα-positive hypereosinophilic syndromes. We describe a fourth patient, a white 14-year-old boy, the third treated with imatinib.

Key Words: hypereosinophilic syndrome, FIP1L1-PDGFRα, myeloproliferative syndrome, childhood, imatinib mesylate

(*J Pediatr Hematol Oncol* 2014;36:e28–e30)

Recently the International Hypereosinophilic Syndromes Working Group revised both the classic definition and the 2008 WHO classification of hypereosinophilic syndromes (HESs).[1] It is suggested that HESs be defined as: (1) blood eosinophilia > 1,500/mm^3 on at least 2 occasions or evidence of prominent tissue eosinophilia associated with symptoms and marked blood eosinophilia and (2) exclusion of secondary causes of eosinophilia. Included in the new classification are 6 categories of HESs and one of these is the myeloproliferative form that has 2 distinct subcategories: myeloproliferative HESs (not clonal) and chronic eosinophilic leukemia, including FIP1L1-PDGFRα-positive (F/P +).

We report a child who was diagnosed as F/P + HES and describe the kinetic of response to imatinib.

CASE REPORT

A 14-year-old male was referred to our department for pallor, weight loss (3 kg in 2 mo), and left shoulder pain (lasting 2 d). On admission he was in good general condition, weight 47 kg, height 166 cm, BSA 1.47 m^2; hepatomegaly (liver 3 cm below the right costal margin), splenomegaly (spleen 8 cm below the left costal margin), and enlarged inguinal (2 cm in maximum diameter) lymph nodes were present. All other lymph nodes were of normal size. The heart and lung findings were within normal limits. Chest x-ray, echocardiography, and electrocardiography were normal.

Blood count showed white blood cells 131,090/mm^3 (neutrophils 80,170/mm^3, eosinophils 49,000/mm^3, lymphocytes 1,030/mm^3, monocytes 440/mm^3, basophils 450/mm^3), Hb 7.7 g/dL, platelets 68,000/mm^3; the peripheral blood eosinophil morphology was normal. Serum level of vitamin B_{12} was 1978 pg/mL (normal range, 200 to 800 pg/mL). Routine blood tests, including IgE, were normal. Stool examination for parasites and screening for serum antibodies against CMV, EBV, *Toxoplasma gondii*, *Toxocara canis*, Leishmania, Borrelia, *Strongyloides stercoralis* were negative.

Bone marrow aspiration showed marked hyperplasia of the myeloid lineage, 35% of which consisted of eosinophil precursors, without signs of dysplasia: the myeloid to erythroid ratio was 70:1 with blast percentage < 5%. Complete immunophenotype assay, CD4/CD8 ratio, and classic bone marrow cytogenetic analysis were normal. A bone marrow biopsy was not performed. The FIPL1-PDGFRα rearrangement [fluorescence in situ hybridization (FISH) positive in 97% of bone marrow cells] was observed. WT-1 amplification, studied in peripheral blood, was 122 copies/ABL copies × 10^4 (normal range, 0 to 15). There was no evidence of the following translocations: bcr/abl t(9;22)(q34;q11), BCR-FGFR1 T(8;22)(p11;q11), TEL-PDGFRβ t(5;12)(q33;p13).

Before the molecular diagnosis was determined, the child was treated for 9 days with hydroxycarbamide (500 mg twice daily PO), but eosinophils slightly increased; the complete blood count on day 9 showed white blood cells 177,610/mm^3 (neutrophils 98,930/mm^3, eosinophils 66,000/mm^3, lymphocytes 5,000/mm^3, monocytes 6,770/mm^3, basophils 910/mm^3). After 14 days of therapy with imatinib (100 mg twice daily PO), clinical condition had returned to normal (disappearance of hepatosplenomegaly); blood count had completely normalized after 40 days of imatinib administration (thrombocytopenia last to resolve). FISH performed 45 days after the beginning of treatment was positive in 2.4% of bone marrow cells; it became completely negative at + 110 days, whereas the nested/RT-PCR had no signal for the first time in a bone marrow aspiration performed on day + 230 (Table 1). At the time of writing, 12 months after the diagnosis, the child is asymptomatic with a persistent complete molecular remission.

MATERIALS AND METHODS

Two-day cultures without stimulation of bone marrow cells were used for cytogenetics and FISH analysis according to standard procedures. A FISH analysis for detection of the 4q12 was performed using the commercially available FIP1L1-CHIC2-PDGFRα (4q12) deletion, break probe (Kreatech Diagnostics, Amsterdam, the Netherlands). For detection of FIP1L1-PDGFRα fusion transcripts, a nested RT-PCR was performed according to Cools et al.[2] Total RNA was extracted from bone marrow cells using TRIzol reagent (Invitrogen, Carlsbad, CA). First-strand cDNA was synthesized from 1 μg total RNA using Mulv reverse transcriptase (Applied Biosystems) with random hexamers according to the manufacturer's instructions. The fusion was

Received for publication May 30, 2012; accepted November 15, 2012.
From the *Pediatric Hematology and Oncology Unit, Oncology Department, A.R.N.A.S. Civico, Di Cristina and Benfratelli Hospitals; ‡Hematology I, A.O. Villa Sofia-Cervello, Palermo; and †Molecular Biology Laboratory, Department of Clinical and Biologic Sciences, University of Turin, San Luigi Gonzaga Hospital, Orbassano, Turin, Italy.
Financially supported by the Parents' association "A.S.L.T.I.-Liberi di Crescere" Onlus.
The authors did not receive funds from National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI).
The authors declare no conflict of interest.
Reprints: Piero Farruggia, MD, Unità Operativa di Oncoematologia Pediatrica, A.R.N.A.S. Civico, Di Cristina e Benfratelli. Piazza Nicola Leotta, 4, 90127 Palermo, Italy (e-mail: pfarruggia@libero.it).

TABLE 1. Molecular and Hematological Monitoring

Day	q-PCR WT1 (ex1-2)	F/P by PCR	F/P by FISH	WBC/mm^3	Eosinophil/mm^3	Hb (g/dL)	Platelet/mm^3
0	122	Positive	97.4	177,610	66,000	8.6	36,000
+ 45	104	Positive	2.34	3,360	40	8.5	68,000
+ 110	26	Positive	Negative	4,810	160	15.0	149,000
+ 230	8	Negative	Negative	4,160	80	15.3	139,000
+ 330	NA	Negative	Negative	9,100	60	14.4	145,000

FISH indicates fluorescence in situ hybridization; NA, not assessed; PCR, polymerase chain reaction; WBC, white blood cells.

analyzed using primers FIP1L1-F4 (5′-acctggtgctgatctttctgat) and PDGFRα-R1 (5′-tgagagcttgtttttcactgga) during the first PCR, and primers FIP1L1-F5 (5′-aaagaggatacgaatgggacttg) and PDGFRα-R2 (5′-gggaccggcttaatccatag) for the second PCR.

DISCUSSION

In 2003 Cools et al[2] identified an F/P fusion gene on chromosome 4q12 in HES patients. The PDGFRα gene encodes the α-chain of the PDGF receptor, a tyrosine kinase receptor class III subtype, which, in the fusion protein, is constitutively activated. The F/P gene can be found, in HESs, in many types of blood cells (eosinophils, neutrophils, basophils, mastocytes, erythrocytes, T lymphocytes, and B lymphocytes)[3]: it is unknown why eosinophil proliferation predominates. F/P + patients can be classified, according to International Hypereosinophilic Syndromes Working Group,[1] as affected by chronic eosinophilic leukemia or, according to WHO 2008, as affected by a myeloproliferative neoplasm associated with eosinophilia.

F/P + individuals suffer typical organ dysfunction with skin, lungs, digestive tract, nervous system, and heart often involved, even though it seems that endomyocardial fibrosis and mucosal ulcerations are more common.[4] Typically the blood count is characterized by leukocytosis, anemia, and thrombocytopenia, tryptase and vitamin B_{12} are elevated and IgE are normal.[5] All these hematological and biochemical aspects (except tryptase, evaluation not performed) were present in our child. He was in good clinical condition, as the other 3 pediatric cases,[6–8] but because of the paucity of cases, not enough information is available to confirm a milder course of the disease in childhood (Table 2). Thrombocytopenia could be a useful tool in differential diagnosis, as it was present in our patient and in 2 out of 3 reported pediatric F/P + patients[7,8] but it is seems exceptional in the rest of pediatric HESs.[8]

TABLE 2. Clinical Characteristics and Treatment of F/P + Patients

References	Sex/Age (y)	Symptoms	Imatinib/ Dose
Rives et al[6]	M/6	Pruritus	No
Rathe et al[7]	F/2	Malaise, fatigue, loss of appetite, pain	Yes/ 300 mg/ m^2 daily
Rapanotti et al[8]	M/16	Splenomegaly, lymphadenopathy, cardiomyopathy	Yes/ 400 mg daily
This study	M/14	Pallor, weight loss, pain, hepatosplenomegaly, inguinal lymphadenopathy	Yes/ 200 mg daily

WT1 gene expression is a useful marker for distinguishing a clonal disease from other HESs and its levels, in our patient, decreased along with the concurrent reduction of FIPL1-PDGFRα transcript (Table 1).

Historically, HESs were treated with steroids, hydroxycarbamide, and interferon-α but, more recently, imatinib, capable of inhibiting the activated PDGFRα at nanomolar concentrations,[9] has become the treatment of choice for F/P + patients. There are only exceptional cases of resistance.[10] The doses range from 100 to 400 mg daily[11] but in literature there are some reports of response maintained with 100 mg even once a week.[12] In the 2 previous pediatric F/P + patients treated with imatinib the dose ranged from 300 mg/m^2 daily to 400 mg/d (Table 2) but we decided to prescribe imatinib at the most common adult dose (200 mg daily). In one of the largest series[11] all 27 adult F/P + patients treated with imatinib had become RT-PCR negative for the FIP1L1-PDGFRα transcripts after 1 to 10 months of therapy. In our case RT-PCR was completely negative after almost 8 months and the boy did not suffer any adverse events. It seems that the response in adult patients is lasting but dependent on treatment, and, when the drug is stopped, the risk of loss of molecular negativity is elevated.[11] Our patient, whose brother is HLA compatible, is in perfect general condition with normal quality of life so, with the parents' agreement, we decided to carry on with imatinib and we plan a slow-dose reduction in the future.

ACKNOWLEDGMENTS

The authors thank native English speaker Frank Adamo for correcting the English.

REFERENCES

1. Simon HU, Rothenberg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome. *J Allergy Clin Immunol*. 2010;126:45–49.
2. Cools J, De Angelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med*. 2003;348:1201–1214.
3. Crescenzi B, Chase A, Starza RL, et al. FIP1L1-PDGFRA in chronic eosinophilic leukemia and BCR-ABL1 in chronic myeloid leukemia affect different leukemic cells. *Leukemia*. 2007;21:397–402.
4. Klion AD, Noel P, Akin C, et al. Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. *Blood*. 2003;101:4660–4666.
5. Kahn JE, Blétry O, Guillevin L. Hypereosinophilic syndromes. *Best Pract Res Clin Rheumatol*. 2008;22:863–882.
6. Rives S, Alcorta I, Toll T, et al. Idiopathic hypereosinophilic syndrome in children: report of a 7-year-old boy with FIP1L1-PDGFRA rearrangement. *J Pediatr Hematol Oncol*. 2005;27:663–665.

7. Rathe M, Kristensen TK, Møller MB, et al. Myeloid neoplasm with prominent eosinophilia and PDGFRA rearrangement treated with imatinib mesylate. *Pediatr Blood Cancer*. 2010;55: 730–732.
8. Rapanotti MC, Caruso R, Ammatuna E, et al. Molecular characterization of paediatric idiopathic hypereosinophilia. *Br J Haematol*. 2010;151:440–446.
9. Carroll M, Ohno-Jones S, Tamura S, et al. CGP 57148, a tyrosine kinase inhibitor, inhibits the growth of cells expressing BCR-ABL, TEL-ABL, and TEL-PDGFR fusion proteins. *Blood*. 1997;90:4947–4952.
10. Simon D, Salemi S, Yousefi S, et al. Primary resistance to imatinib in Fip1-like 1-platelet-derived growth factor receptor alpha-positive eosinophilic leukemia. *J Allergy Clin Immunol*. 2008;121:1054–1056.
11. Baccarani M, Cilloni D, Rondoni M, et al. The efficacy of imatinib mesylate in patients with FIP1L1-PDGFR alpha-positive hypereosinophilic syndrome. Results of a multicenter prospective study. *Haematologica*. 2007;92:1173–1179.
12. Helbig G, Stella-Holowiecka B, Grosicki S, et al. The results of imatinib therapy for patients with primary eosinophilic disorders. *Eur J Haematol*. 2006;76:535–536.